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Azacitidine results in comparable outcome in newly diagnosed AML patients with more or less than 30% bone marrow blasts

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ABSTRACT

The efficacy of azacitidine has been demonstrated in acute myeloid leukemia (AML) patients with 20–30% bone marrow (BM) blasts, but limited data is available on patients with ≥30% blasts. We analyzed 55 newly diagnosed AML patients, treated with azacitidine. The overall response rate was 42%. Median overall survival (OS) was 12.3 months. We confirmed poor-risk cytogenetics, therapy-related AML, performance score ≥2, and white blood cell count $\geq 15 \times 10^9$/L as independent adverse predictors for OS. The BM blast percentage, however, had no impact on OS ($P = 0.55$).

In conclusion, administration of azacitidine is effective in AML patients with 20–30% and >30% BM blasts.

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1. Introduction

Acute myeloid leukemia (AML) is a heterogeneous clonal disorder of hematopoietic progenitor cells with different molecular genetic abnormalities, clinical characteristics, and variable outcomes with currently available treatment [1,2]. AML is most common in the elderly with a median age at presentation of approximately 70 years [2]. Older AML patients generally have a limited benefit with currently available treatment due to a combination of poor chemotherapeutic tolerance and inherent disease resistance [3–10]. Nevertheless, several studies on intensive and non-intensive treatment types suggest that older AML patients benefit from treatment [11,12].

Recently, azacitidine has become available for (older) AML patients with 20–30% bone marrow (BM) blasts. A phase 3 study demonstrated that azacitidine significantly improved OS in higher-risk MDS patients compared to best supportive care and low-dose cytarabine [13]. A post hoc analysis of this study showed improved OS in the subgroup of AML patients with 20–30% blasts treated with azacitidine compared with best supportive care [14]. The efficacy of azacitidine in previously untreated AML patients has been confirmed in a retrospective analysis of an Italian compassionate program and in a small German prospective multicenter study [15,16]. However, until now no comparison of treatment outcome has been made between AML patients with 20–30% BM blasts, for whom azacitidine is generally available, and patients with 30% or more BM blasts, who can only be treated off-label. Therefore, we analyzed the treatment results of 55 newly diagnosed AML patients who have been treated with azacitidine.

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2. Patients and methods

2.1. Patients and data collection

After FDA approval of azacitidine in the US and before EMA approval in the EU, a compassionate named patient program (NPP) was initiated in the Netherlands for MDS, CMML, and AML patients with 20–30% blasts. The results of this Dutch NPP have been reported [17]. In the present retrospective study, the NPP was extended and an analysis was made of 55 consecutive newly diagnosed AML patients (with 20–30% and >30% BM blasts) who have been treated upfront with azacitidine. Data of this extended compassionate NPP has been collected between August 2010 and March 2012 after informed consent in accordance with the Declaration of Helsinki by studying health records. Diagnoses were made using World Health Organization (WHO)-2008 criteria [18]. Cytogenetic risk could be determined in 52 of 55 patients according to the refined cytogenetic classification of the Medical Research Council [19]. The BM blast count refers to myeloblasts or monoblasts.

2.2. Treatment

Azacitidine was administered subcutaneously at the approved schedule of 75 mg/m^2/day during 7 days every 28 days. Physicians intended to give at least 6 cycles of treatment. Patients who responded well were to continue treatment until progression. Red blood cell (RBC) transfusions were given in agreement with general recommendations: Hb <8 g/dL. RBC transfusion dependency was defined as receiving ≥2 RBC transfusions every 8 weeks.

2.3. Response criteria and study endpoints

Response was evaluated after every cycle by blood count and by bone marrow aspirate if available. All patients had received a bone marrow aspirate at diagnosis. Morphologic complete remission (CR), CR with incomplete blood count recovery (CRi), and partial remission (PR) were defined according to IWG-2003 criteria for AML [20]. Hematological improvement of the erythroid, neutrophil, and platelet lineages was defined by IWG-2006 criteria [21]. Overall survival (OS) was defined as the time from onset of azacitidine treatment to death. Patients who remained alive were censored at the last visit to the hospital.

2.4. Statistical analysis

Analyses were made on an intent-to-treat basis. Differences between groups in patient characteristics and response rates were compared using 2-sided Fisher's exact tests or chi-square tests for categorical variables and Student's *t*-tests or Mann–Whitney *U* tests for quantitative variables. Survival curves were estimated with the Kaplan–Meier method. Predictive factors for OS were analyzed by Wald tests for univariate and multivariate comparisons. Cox proportional hazards regression models were used to estimate hazard ratios and associated 95% confidence intervals (CI). A *P*-value < 0.05 was considered significant. SPSS-19 was used for analysis.

3. Results

3.1. Baseline characteristics of the study population

The study population included 55 newly diagnosed and previously untreated AML patients from 12 different hospitals. Baseline characteristics are depicted in Table 1. Median age was 73 years (range 59–84). The median BM blast count was 25% (14–85%); 38 (69%) patients had <30% BM blasts and 17 (31%) patients had ≥30% BM blasts. There were no significant differences in baseline characteristics between patients with <30% and ≥30% BM blasts (Table 1).

3.2. Response to treatment and overall survival

The median number of azacitidine cycles was 6 (range 1–27) (Table 2). Response was achieved in 23 (42%) patients, including 13 (24%) CR, 4 (7%) CRi, and 6 (11%) PR. Hematological improvement was achieved in 23 (42%) patients, of whom 15 patients had improvement of the erythroid lineage, 19 of the platelet lineage, and 7 of the neutrophil lineage, with combined responses of two or three lineages in 16 patients. Three patients had peripheral blood counts that were too high at baseline to evaluate the hematological improvement. Four patients had hematological improvement, but achieved no CR or PR. Median time to response was 4 months (range 1–10) and median time to hematological improvement was 2 months (range 1–7). Duration of response ranged from 9 to at least 27 months. Median duration of response was not reached; response was ongoing in 14 patients at the end of study. Transfusion dependency was present in 33 (61%) patients at baseline and 14 patients became transfusion dependent during the first two cycles. After 1 to 6 cycles, 14/47 (30%) patients became transfusion independent.

Failure to complete at least 3 cycles of azacitidine was reported in 16 (29%) patients. The reasons for discontinuation were disease

Table 1
Baseline patient characteristics by BM blast count; results are reported as *N* (%) or median (range). *Abbreviations:* BM, bone marrow; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; WBC, white blood cell count; LDH, lacate dehydrogenase; WHO, world health organization. § One patient with 27% BM blasts had myelofibrosis with a high leukocyte count of 146 × 10^9/L including 70 × 10^9/L peripheral blasts at baseline.

	All patients (*N* = 55)	<30% BM blasts (*N* = 38)	≥30% BM blasts (*N* = 17)	*P*
Age (years)				0.15
Median (range)	73 (59–84)	72 (60–84)	75 (59–82)	
Sex				1.00
Female	14 (25%)	10 (26%)	4 (24%)	
AML, type				0.50
De novo	34 (62%)	25 (66%)	9 (53%)	
Previous MDS	11 (20%)	6 (16%)	5 (29%)	
Therapy related	10 (18%)	7 (18%)	3 (18%)	
Cytogenetic risk				0.53
Favorable	4 (4%)	2 (6%)	0 (0%)	
Intermediate	33 (64%)	21 (60%)	12 (71%)	
Poor	17 (33%)	12 (34%)	5 (29%)	
BM blasts (%)				<0.001
Median (range)	25 (14–85)	22 (14–29)	48 (31–85)	
Circulating blasts				0.36
Absent	19 (35%)	15 (39%)	4 (24%)	
Present	36 (65%)	23 (61%)	13 (76%)	
WBC (×10^9/L)				
Median (range)	3 (0–146§)	3 (0–146§)	2 (0–61)	0.44
≥15 × 10^9/L	12 (22%)	8 (21%)	4 (24%)	1.00
LDH				1.00
Increased	26 (51%)	18 (51%)	8 (50%)	
Transfusion dependency				0.56
Present	33 (61%)	24 (63%)	15 (53%)	
WHO performance score				0.72
0–1	41 (79%)	29 (81%)	12 (75%)	
2–4	11 (21%)	7 (19%)	4 (25%)	

Table 2
Treatment outcome by BM blast count; results are reported as *N* (%) or median (range). *Abbreviations:* BM, bone marrow; CR, complete remission; CRi, CR with incomplete blood count recovery; PR, partial remission; HI, hematological improvement; CI, conficence interval; NR, not reached.

	All patients (*N* = 55)	<30% BM blasts (*N* = 38)	≥30% BM blasts (*N* = 17)	*P*
Number of azacitidine cycles	6 (1–27)	6 (1–27)	5 (1–24)	0.96
<3 cycles	14 (26%)	10 (26%)	4 (24%)	0.83
Response, overall	23 (42%)	16 (42%)	7 (41%)	1.00
CR	13 (24%)	10 (26%)	3 (18%)	0.81
CRi	4 (7%)	2 (5%)	2 (12%)	
PR	6 (11%)	4 (11%)	2 (12%)	
Hematological improvement (HI)	23 (42%)	15 (39%)	8 (47%)	1.00
Time to response (months)	4 (1–10)	4 (2–10)	4 (1–6)	0.28
Time to HI (months)	2 (1–7)	2 (1–4)	2 (1–7)	0.63
Overall survival (months) (95% CI)	12.3 (7.8–18.0)	14.3 (7.8–20.6)	11.7 (1.5-NR)	0.55

progression and/or early death (*N* = 12), side-effects (pancytopenia and fever; *N* = 2), and consent withdrawal (*N* = 2). Dose adjustments or schedule changes were made in 15 (27%) patients, of which 11 before the sixth treatment cycle. Schedule change from 7 to 5 days was applied in 9 patients; dose reductions of 50% were applied in 4 patients, and 2 patients had dose reductions of 33% and 25%.

No differences in response rates (CR, CRi, PR) or hematologic improvement rates were found in patients with <30% versus ≥30% BM blasts (Table 2). Median OS of all patients was 12.3 months (95% CI 7.8–18.0 months). Patients with ≥30% BM blasts did not have a survival disadvantage (Table 2). Responders had a longer OS than non-responders (median OS 24.3 versus 4.5 months, $P < 0.001$; Fig. 1A). Since it generally takes several cycles to achieve a response, we compared also the patients who completed at least three cycles of azacitidine. This analysis also demonstrated a longer median OS in responders compared to non-responders (24.3 versus 9.7 months, $P < 0.001$; Supplementary Fig. 1). The OS in responders and non-responders was independent of the BM blast percentage ($P = 0.33$ and $P = 0.47$, respectively; Fig. 1B).

Interestingly, of the 17 patients with poor-risk cytogenetics, four achieved a response (3 CR, 1 PR), which was associated with an improved OS compared to non-responding poor-risk patients (14.3 versus 3.7 months; $P = 0.01$), illustrating the efficacy of azacitidine also in patients with poor risk cytogenetics.

3.3. Predictors for overall survival

We analyzed potential predictors for OS that were selected based on previous studies [2,22]. Univariate analysis revealed no difference in OS in patients with <30% versus ≥30% BM blasts (Table 3a; Fig. 2A). In contrast, in univariate analysis, poor OS was associated with poor-risk cytogenetics, therapy-related AML, and WHO performance score ≥2 (Table 3a; Fig. 2B–D). Based on our previous experience, we were also interested in the predictive value of platelet doubling after the first cycle of azacitidine [17]. However, only 4 patients showed a platelet doubling after the first cycle of azacitidine. Therefore, platelet doubling was not included in further analyses.

For multivariate analysis, we selected predictors for OS with $P < 0.15$ in univariate analysis. Multivariate analysis confirmed poor-risk cytogenetics, therapy-related AML, baseline WHO performance score ≥2, and baseline WBC $\geq 15 \times 10^9$/L as independent adverse predictors for OS (Table 3b, Fig. 2E).

In addition, we assessed in our cohort of AML patients the azacitidine-specific prognostic scoring system that was designed and validated for higher-risk MDS patients and AML patients with 20–30% BM blasts [17,22]. The azacitidine-specific prognostic score was determined as follows: one point was assigned to performance score ≥2, presence of circulating blasts, RBC transfusion dependency of ≥4 units/8 weeks, and intermediate-risk cytogenetics; and two points were assigned to poor-risk cytogenetics. The score could be determined in 47 patients who could subsequently be divided into low- (score 0; *N* = 0), intermediate- (score 1–3; *N* = 37), and high (score 4–5; *N* = 10) risk groups. Median OS was 12.7 months in the intermediate-risk group versus 4.1 months in the high-risk group ($P = 0.013$) (Supplementary Fig. 2). In our cohort, the risk score predicted OS in patients with 20–30% BM blasts, as was shown before

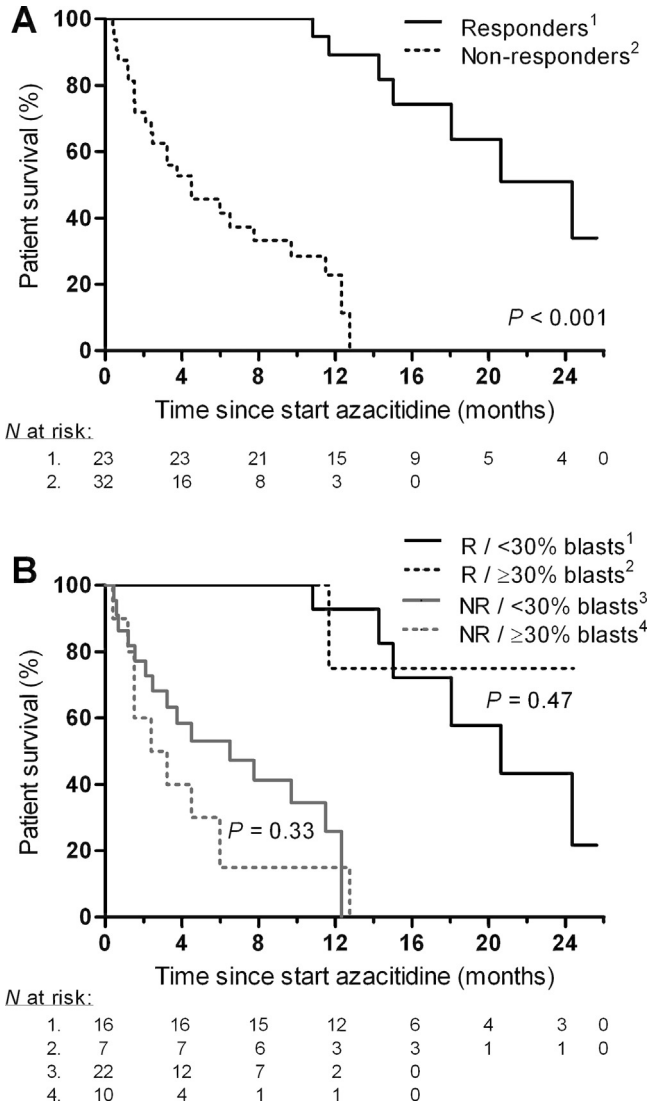

Fig. 1. Patient survival by response to azacitidine. (A) Median OS was significantly better in responders compared to non-responders (24.3 versus 4.5 months; $P < 0.001$). (B) The BM blasts percentage had no impact on OS in responders (R) or non-responders (NR).

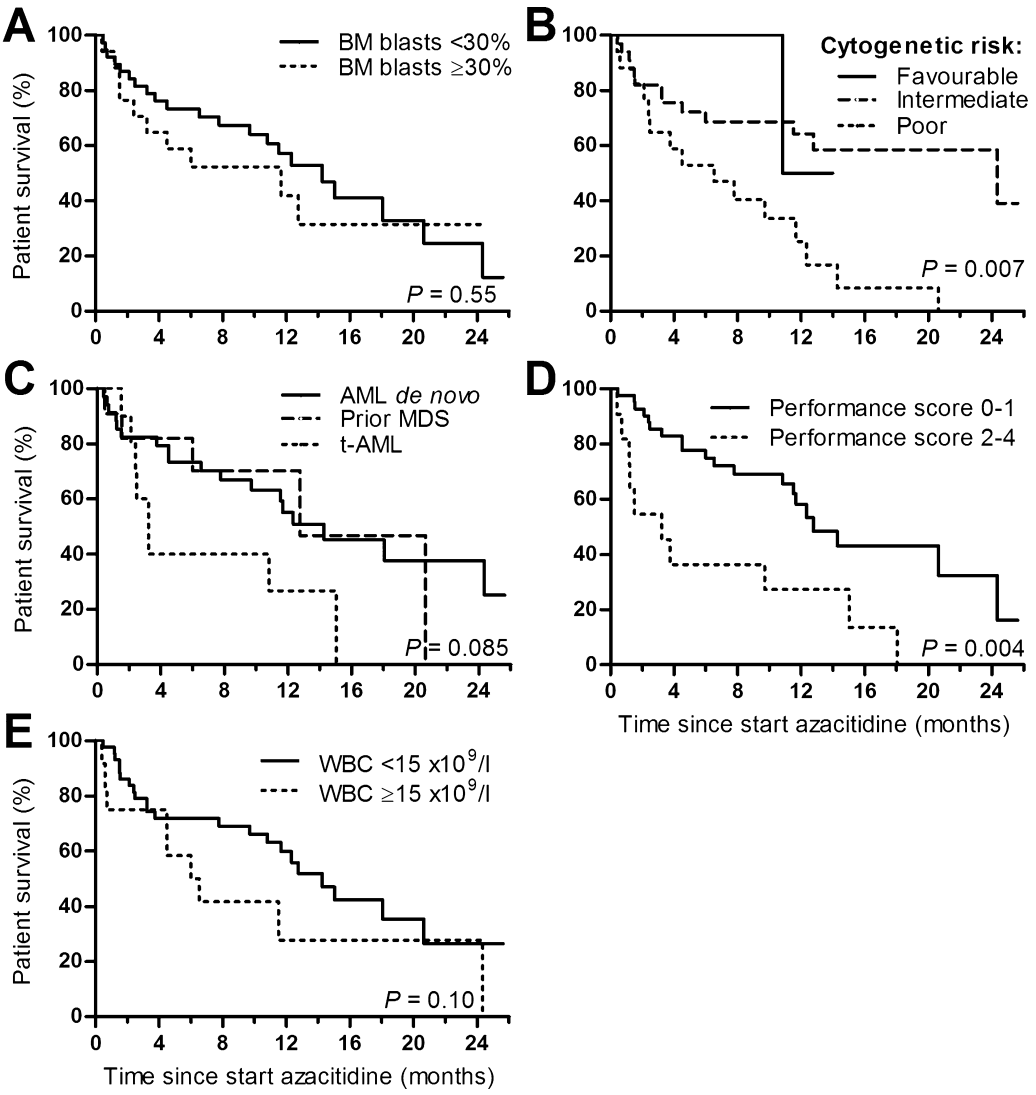

Fig. 2. Impact of risk factors on survival of all patients. (A) BM blasts <30% versus ≥30%. (B) Cytogenetic risk score. (C) AML de novo versus prior MDS versus therapy-related AML (t-AML). (D) WHO performance score 0–1 versus 2–4. (E) WBC <15 versus $\geq 15 \times 10^9$/L.

[17,23], and also significantly predicted OS in the subgroup with ≥30% BM blasts ($P = 0.006$).

4. Discussion

In this multicenter retrospective analysis, 55 patients with newly diagnosed and untreated AML received azacitidine for a median of 6 cycles. In 42% of the patients a response was achieved, including 24% CR. These response rates are comparable with the results of the AML patients in the AZA-001 trial (18% CR), with the previously untreated AML patients enrolled in an Italian compassionate program (overall response 50%), and with the previously untreated AML patients included in a German prospective multicenter trial (overall response 48%) [14–16]. Further, in our study the median OS was 12.3 months, which was less than the 24.5 months in the AZA-001 trial, but superior compared to the 9 months observed in the untreated patients in the Italian NPP and 7.7 months in the German trial [14–16]. Altogether, these data show that the efficacy of azacitidine in newly diagnosed AML patients can also be confirmed by the extended Dutch NPP. Interestingly, also patients with poor-risk cytogenetics may benefit from azacitidine treatment. Indeed, in our study, 4 of 17 patients with poor-risk cytogenetics showed a response to azacitidine which was associated with an improved OS.

Although azacitidine is currently only registered for the treatment of AML with 20–30% BM blasts, no differences in survival and response rates were observed in patients with <30% and ≥30% BM blasts. The ongoing AML-001 trial, which compares azacitidine with intensive chemotherapy or best supportive care in AML patients with ≥30% blasts, should be awaited to confirm our observations in a prospective randomized clinical trial. The earlier mentioned German and Italian studies did not compare the efficacy of azacitidine based on the percentage of BM blasts [15,16]. Factors that, in contrast to the percentage of BM blasts, significantly and independently predicted for OS were cytogenetic risk status, AML type (therapy-related), baseline WBC, and WHO performance score.

Identification of patients who are likely or unlikely to benefit from azacitidine treatment is, besides from a scientific- and patient perspective, also an important issue in managing the costs of healthcare. Therefore, it would be of help to have response predictors. In the French NPP, in a cohort of 282 higher-risk MDS patients, four routine factors have been identified that were predictive for OS. The prognostic relevance of these factors (WHO performance score, circulating blasts, RBC transfusion dependency,

Table 3
Predictors for overall survival: univariate and multivariate analysis. *Abbreviations:* OS, overall survival; HR, hazard ratio; CI, confidence interval; AML, acute myeloid leukemia; WBC, white blood cell count; LDH, lacate dehydrogenase; ref., reference group; NR, not reached.*Significant difference.

	Median OS (months)	HR (95% CI)	*P*
(a) *Univariate analysis*			
Bone marrow blasts			0.55
<30%	14.3	ref.	
≥30%	11.7	1.3 (0.59–2.7)	
Cytogenetic risk			<0.008*
Favorable	NR	1.1 (0.1–8.8)	0.91
Intermediate	10.2	ref.	
Poor	2.6	3.1 (1.5–6.8)	0.003*
AML, type			0.086
De novo	14.3	ref.	
Previous MDS	12.7	1.0 (0.38–2.8)	0.96
Therapy related	3.2	2.5 (1.1–5.9)	0.038*
WHO performance score			0.006*
0–1	12.7	ref.	
≥2	3.2	3.0 (1.4–6.5)	
WBC			0.11
$<15 \times 10^9$/L	14.3	ref.	
$\geq 15 \times 10^9$/L	6.0	1.9 (0.86–4.2)	
LDH			0.34
Normal	12.3	ref.	
Increased	11.5	1.4 (0.69–2.9)	
Circulating blasts			0.44
Absent	15.0	ref.	
Present	11.5	1.4 (0.6–2.9)	
Transfusion dependency			0.17
No	18.0	ref.	
Yes	11.5	1.7 (0.80–3.8)	
(b) *Multivariate analysis*			
Cytogenetic risk			0.001*
Favorable	NR	0.12 (0.01–1.2)	0.073
Intermediate	10.2	ref.	
Poor	2.6	3.9 (1.6–9.3)	0.002*
AML, type			0.002*
De novo	14.3	ref.	
Previous MDS	12.7	2.1 (0.68–6.8)	0.19
Therapy related	3.2	8.9 (2.7–29.3)	<0.001*
WHO performance score			<0.001*
0–1	12.7	ref.	
≥2	3.2	7.3 (2.6–20.0)	
White blood cells			0.003*
$<15 \times 10^9$/L	14.3	ref.	
$\geq 15 \times 10^9$/L	6.0	5.3 (1.7–15.8)	

and cytogenetic risk) could be confirmed in our cohort of 55 untreated AML patients and might be of benefit for the design of future trials.

Finally, the treatment of older AML patients is clinically challenging. Our data on 55 newly diagnosed and previously untreated AML patients suggest that administration of azacitidine to older AML patients is feasible and also has a favorable impact on outcome in patients with more than 30% BM blasts.

Conflict of interest statement

J.K. is a Celgene employee. G.H. and A.A.v.d.L. received consultancy fee from Celgene. All remaining authors have no conflict of interest to report.

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Contributions: L.H.v.d.H.: provided the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the manuscript, revised it critically for important intellectual content, and gave final approval of the version to be submitted; N.J.G.M.V.: supplied the analysis and interpretation of data; M.v.M.K., A.B., O.d.W., M.d.G., C.A., M.H., L.L., and A.A.v.d.L.: enrolled patients and provided acquisition of data; J.K.: provided the medicine for study; E.V. and G.H.: provided the conception and design of the study, interpretation of data, drafting the manuscript, revised it critically for important intellectual content, and gave final approval of the version to be submitted.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.leukres.2013.03.022.

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